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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: FRANZ Michel
Appl. No.	: 10/789,174
Filed	: February 26, 2004
For	: STABILIZED PHARMACEUTICAL COMPOSITION COMPRISING AN EXTENDED RELEASE NOW-STEROIDAL ANTI-INFLAMMATORY AGENT AND AN IMMEDIATE RELEASE PROSTAGLANDIN
Examiner	: SILVERMAN, ERIC
Group Art Unit	: 1619

DECLARATION UNDER 37 C.F.R § 1.132

Mail Stop Amendment

Commissioner for Patents
P.O Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This Declaration is being submitted in further support of the demonstration that claimed invention unexpectedly provides increased stability of pharmaceutical composition comprising an extended release non steroidal anti-inflammatory agent and an immediate release prostaglandin.
2. I am an inventor on the above-identified patent application and am familiar with the rejections made in the Office Actions of 12 May 2006, 11December 2006, 13 March 2007 and 11 May 2007.
3. I have extensive experience in the field of the claimed invention as indicated in the attached Curriculum Vitae provided herewith as Exhibit A.

4. I have conducted a stability study during a period of 6 months. Hard capsules made of gelatine and made of Hydroxyl-Propyl-Methyl-cellulose (HPMC) (containing extended release non-steroidal anti-inflammatory agents and an immediate release prostaglandin) were compared. The protocol of this study and the results of this study were presented in the Exhibit B.

5. The capsules used in the stability study were same size hard capsules made (supplier : Capsugel) of gelatine or of hydroxypropylmethylcellulose (supplier : Shionogi). One batch of Misoprostol mini-tablets was made, according to the formulation :

Misoprostol dispersion 1% in HPMC	20.0mg
Microcristalline cellulose	35.9mg
Crospovidone	8.0mg
Colloidal Silicon Dioxide	0.1mg
Hydrogenated castor oil	1.0mg

One batch of Diclofenac Sodium pellets was available according to the formulation:

Diclofenac Sodium	75.0mg
Microcristalline cellulose	15.0mg
Lactose	26.0mg
Kollidon K25	7.5mg
Sucrose stearate	6.5mg
Methacrylate esters copolymer	4.7mg
Talc	2.4mg
Hydroxypropylmethylcellulose	0.5mg

The two types of hard capsules were filled with one mini-tablet of misoprostol and Diclofenac Sodium pellets.

The data gathered during the stability study have demonstrated that the misoprostol mini-tablets contained in the hard hydroxypropylmethylcellulose capsules are offering a significantly better stability compared to hard gelatine capsules.

6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: May, 27th 2007

By: _____
Michel FRANZ

EXHIBIT A

Michel FRANZ
avenue du Haut-Champ,52
B-1082 Brussels
michel.franz@skynet.be
Tel: 32(0)2 4654434 Cell Phone: 32(0)2 497 421363 Fax: 32(0)2 4694855

Profile

When graduated as a Pharmacist at Liège University (Belgium), I had two major areas of interest: Pharmacognosy and Pharmaceutical Technology.

I started with 2 years in Congo/Zaire at the University of Kinshasa (instead of military service) and came back in Belgium to begin a career in the Pharmaceutical Industry.

My first responsibilities were in manufacturing but I managed to move progressively to Pharmaceutical Development responsibilities.

I had the opportunity to work for several important pharmaceutical companies including Baxter, Laboratoires Thissen, UCB Pharma, Monsanto/ Searle, Lilly and Janssen Research Foundation, accumulating a broad experience in the early pharmaceutical development activities as well as the late stage technology transfer.

In parallel to my professional career, I was able to develop an interesting network in Belgium and abroad (Universities, Health and Business Authorities, Industrial Pharmacists, Excipients and Active Ingredients Suppliers, Machine Manufacturers) .

Personal informations

- Date of birth: 2 september 1945
- Nationality: belgian
- Education :
  University of Liège (1963-1968) : Pharmacist , Magna Cum Laude
  University of Brussels(1981-1982) : Solvay Business School Certificate
- Languages:
  French , mother language
  English , good spoken and written
  Dutch: good spoken

Miscellaneous

-Elected on the list of Industrial Pharmacists of the Belgian Health Ministry, n°598 (Qualified Person to release pharmaceutical products in the European Community)

-Visiting Professor and co-founder of the post -graduate teaching in Industrial Pharmacy organised by the 3 French speaking Universities in Belgium.

-Past Chairman and current member of the board of UPIP VAPI (Belgian Industrial Pharmacists Professional Association) and past national representative to the European Federation of sister associations.

-Active member in several professional and scientific other organisations

-Author or co-author of several publications and patents

-Good knowledge of the retail pharmacy and hospital pharmacy activities in Europe and Africa

Michel FRANZ CURRICULUM VITAE

Experience and Achievements

From beginning of 1999- today- FRANPHARMA sprl
- *Consultant* in Pharmaceutical Product Development
- Missions in Belgium, France, The Netherlands, North Africa and the US.

1996 to January 1999-**Janssen Research Foundation** (Beerse)
- *Senior Project Manager*
- I had to coordinate pharmaceutical product development activities on projects being worked out intra the company or in collaboration with Drug Delivery Companies

1993-1996-**Lilly Development Centre** (Mont-Saint-Guibert)
- *Scientific Advisor*
- The function included the following responsabilities:
  Advice to the Pharmaceutical Development activities
  Contacts to identify opportunities in the field of Drug Delivery Systems
  Improvement of the network with Universities and other official bodies in Belgium and in Europe

1978-1993-**Continental Pharma / Monsanto/ Searle** (Louvain-la--Neuve)
- Management positions in (bio)pharmaceutical development, R&D
  Last: *Senior Director*, European Pharmaceutical Development
- The function included the following responsabilities (analytical & technological):
  Pre-formulation, formulation for New Chemical Entities
  Design of new formulations for existing products
  Manufacturing and Quality Control of dosage forms used during clinical trials
  Packaging of clinical supplies for international studies (shipment to 40 countries)
  Technology Transfert to manufacturing sites in France, UK, Puerto Rico , Germany
  Participation to the selection of manufacturing equipment and Plant design for Manufacturing and Control
  Preparation of the CMC section of regulatory affairs documents for worldwide applications
- The biggest project we finalised is Arthrotec, a patented core tablet (US 5,015,481) with cumulated sales well over 1 billion $!

1974-1978- **UCB Pharma** (Brussels and Braine-l'Alleud)
- *Pharmaceutical Technology Manager*
- I have (re)formulated several key products, including Nootropil tablets
- The job gave me the opportunity to work in both Manufacturing & Control and R & D environments.

1972-1974- **Laboratoires Thissen** (Therabel Group) Uccle
- *Manufacturing Supervisor*
- In a short period of time I was able to gather a good experience as the company is working as a contract lab. The diversified nature of the products was giving me a prime chance to solve formulation issues .

1971-1973- **Baxter-Travenol** (Lessines)
- *Quality Control Supervisor*
- I was exposed early in my career to the concept of the GMPs, in a state of the art plant built to produce Large Volume Parenterals and other hospital products.

1969-1971- **University of Kinshasa** (Zaire)
- *Lecturer at the School of Pharmacy*
- In addition to teaching I was doing research on endemic plants (Strychnos and Dioscoreas).

Exhibit B

A stability study has been performed during a period of 6 months. Capsules made of gelatine of hydroxypropylcellulose (HPMC) containing Extended Release Diclofenac Sodium pellets and one Immediate Release Misoprostol mini-tablet were compared.

The attention was focused on the stability of Misoprostol as it is a very sensitive compound. The analytical methodology to assay Misoprostol and the impurities was based on the monograph recently published in the European Pharmacopeia (monograph 1731, January 2006).

The moisture of the Misoprostol mini-tablets was designed to be high to accelerate the degradation of Misoprostol and to facilitate the evidence of the possible difference between the 2 types of capsules. The mini-tablets moisture results were : 7;44% in the gelatine capsules and at 7.98% in the HPMC capsules.

Both types of capsules were packaged in aluminium-aluminium blisters which are offering an excellent protection against atmospheric agents during the storage.

We report the results obtained on packaged capsules stored at 30°C/65% Relative Humidity and 40°C/75% Relative Humidity.

The comparison of the data indicates clearly that the use of HPMC capsules offers a clear advantage over the gelatine capsules for the stability of the prostaglandin.

Condition : + 30°C/65% RH

Timepoint (months)	Misoprostol Content (mg)	Misoprostol Content (% of label claim)	Total Epimers	Misoprostol A	Misoprostol B	Total impurities
Gelules gelatine						
0	0,193	96,7	0,68	0,14	nd	0,82
1	0,197	98,3	0,93	0,46	0,04	1,45
3	0,191	95,7	1,19	0,87	0,15	2,21
6	0,188	94	1,85	1,90	0,62	4,37
Gelules HPMC						
0	0,191	95,5	0,77	0,12	nd	0,89
1	0,197	98,6	1,04	0,39	0,01	1,44
3	0,195	97,4	1,34	0,66	0,03	2,03
6	0,191	95,7	1,01	1,20	0,08	2,29

Condition : + 40°C/75% RH

Timepoint (months)	Misoprostol Content (mg)	Misoprostol Content (% of label claim)	Total Epimers	Misoprostol A	Misoprostol B	Total impurities
Gelules gelatine						
0	0,193	96,7	0,68	0,14	nd	0,82
1	0,192	95,8	1,63	2,12	0,66	4,41
3	0,175	87,6	2,43	4,07	2,37	8,87
6	0,151	75,5	4,33	6,94	6,03	17,30
Gelules HPMC						
0	0,191	95,5	0,77	0,12	nd	0,89
1	0,197	98,7	1,18	1,63	0,09	2,90
3	0,186	93,1	1,69	3,53	0,23	5,45
6	0,174	87,1	1,87	7,66	0,62	10,14

Impurities are expressed in % of the theoretical amount of Misoprostol.

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